Methodological Errors in "Treatments for Acute Pain – A Systematic Review" (AHRQ)

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Abstract:

This paper expands on comments by the author, offered to a September 2020 circulated draft of Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review 240, titled "Treatments for Acute Pain: A Systematic Review" **[Ref 1, Ref 2].** Author's original comments to the draft were transmitted online to AHRQ and by email to the Director and senior staff of the Agency. This updated communication presents the evidentiary basis for a mandatory and substantial revision of Comparative Effectiveness Review 240 by AHRQ, followed by a window for public comments, before its republication. There is no other recourse to mitigate stigmatizing depictions of patients in pain who require opioid analgesia and misleading interpretations of the available opioid trials that characterize the present published review.

Analysis of Medical Evidence

From the AHRQ Report Structured Abstract: "Meta-analyses were conducted on pharmacologic therapy for dental pain and kidney stone pain, and likelihood of repeat or rescue medication use and adverse events…."

"Results: One hundred eighty-three RCTs on the comparative effectiveness of therapies for acute pain were included. Opioid therapy was probably less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) for surgical dental pain and kidney stones, and might be similarly effective as NSAIDs for low back pain."

Author's comments:

Study Design [Ref 3,4]

In meta-analyses, mean changes from baseline to post-treatment on pain measures are pooled for the opioid and comparator, from which pooled opioid–comparator group differences are derived.

Randomized controlled trials (RCTs) and meta-analyses measure central tendency, with a core assumption and necessary pre-condition being normal distribution (e.g., the "bell-shaped curve") in treatment/comparator/placebo response. e.

Analgesic response in chronic pain patients shows bimodal distribution with pain reduction substantial or near-absent/absent. Bimodal distribution in opioid response appears within 2-4 weeks of randomization and treatment initiation.

A clinical population with bimodal distribution in treatment response violates the core assumption of normal distribution in RCTs and meta-analyses.

Meta-analyses and systematic reviews, when appropriately used, are powerful tools for understanding efficacy and safety in many areas of medicine. However, few understand they are not useful in analgesic response. With meta-analyses and systematic reviews, the authors decide what is "evidence." Roger Chou was a lead author of the 2016 CDC Guideline and its derivative systematic review – a document considered by many medical professionals to be the exemplar of conclusions based on evidence selected and defined with prejudicial intent.

The conclusions of the AHRQ review are not helpful to clinicians treating pain patients. Meta-analyses and systematic reviews in chronic pain have concluded that compared to placebo, there is little or no pain efficacy benefit with NSAIDs, acetaminophen, antidepressants (duloxetine, amitriptyline) or gabapentinoids (gabapentin, pregabalin).

Opioid Selection [Ref 6-8]

Excluding (1) trials in acute renal colic pain with parenteral delivery of opioid and nonopioid, and (2) trials comparing opioid agonists to multimodal (e.g., tapentadol) or partial agonist (e.g., buprenorphine) opioids, 47 trials reported in this review compared opioids to NSAIDs or acetaminophen, with codeine or tramadol as the selected opioid:

All oral opioid vs NSAIDs or acetaminophen comparisons: 38 of 47 trials (80.8%)

Acute post-operative pain: 5 of 11 trials (45.5%)

Acute low back, musculoskeletal, and dental pain: 33 of 36 trials (91.6%)

Thus, in trials comparing opioids to NSAIDs or acetaminophen (excluding parenteral delivery), the selected opioid was codeine or tramadol in 80.8% of trials overall, and in 91.6% of acute low back, musculoskeletal, and dental pain trials. There are several implications:

Codeine and tramadol are both weak opioid analgesics. Both require hepatic enzymatic conversion to an active analgesic metabolite. A significant proportion of the population possesses a genetic variation of cytochrome 2D6. Consequently, these individuals poorly convert codeine or tramadol, and experience side effects rather than analgesia. For this reason, codeine has fallen into relative disuse.

This genetic variation in CYP450 expression alters opioid pharmacokinetics and may contribute to bimodal distribution in opioid response, along with pharmacodynamic variation and other factors.

Codeine and tramadol account for most (80.8%) oral opioid comparisons to NSAIDs or acetaminophen, and nearly all (91.6%) in acute low back, musculoskeletal, and dental pain. This needs to be stated clearly in the report:

"Weak Prodrug Opioids Accounted for >80% of Oral Opioid Comparisons to NSAIDs or Acetaminophen Overall, and 91.6% in Acute Low Back, MSK and Dental Pain."

Obvious, yet repeatedly ignored in this and other AHRQ reviews authored by Chou et al., is that meta-analyses are unsuited for evaluating the efficacy of opioids, which require a tailored approach to balance response and side effects.

Additional Discussion

From the AHRQ Report Background:

"The key decisional dilemma in acute pain management involves selection of interventions to provide adequate pain relief, in order to improve quality of life, improve function, and facilitate recovery, while minimizing adverse effects and avoiding overprescribing of opioids.8 Evidence also suggests that adequate acute pain treatment may mitigate factors that promote the transition to chronic pain.3,9,10 However, shortcomings in acute pain care have been documented.11,12 In addition to the underlying cause of pain, patient factors that impact acute pain management include age, sex, race/ethnicity, pain severity, comorbidities (including mental health and substance use), genetic factors, pregnancy, or breastfeeding status.13-16 Timing of presentation and clinical setting can also influence acute pain management. For example, postoperative pain occurs at a specific point in time and is often managed with multimodal strategies in a monitored setting prior to discharge, whereas in outpatient clinic settings, timing of presentation of acute pain is variable, and assessing treatment response is often not feasible. Additionally, access and care options may vary.2,8 Different acute pain conditions (e.g., musculoskeletal pain, neuropathic pain, or visceral pain) may respond differently to treatments. Therefore, a treatment that is effective for one acute pain condition and patient in a particular setting may not be effective in others." [Reference numbers in the original report]

Author's Comments: It is highly revealing that despite this acknowledgement of the complexities of evaluating pain therapies, the AHRQ authors proceed to merge data of doubtful quality and to generalize their conclusions using terms such as "probably"

and “might be”. A section on “Research Gaps” in both the draft and the final report briefly mentions a wide range of confounding factors – which are then ignored as the authors race to their pre-ordained conclusions, attempting to disqualify prescription opioid analgesics from use in acute pain.

A far more supportable conclusion from this review is that the present state of medical literature lacks sufficient rigor and repeatability to arrive at any conclusions at all.

In this context, the following observations apply:

1. While the investigators’ desire to limit the scope of their “comprehensive review” is understandable, exclusion of German language studies from the AHRQ review is a significant omission. The German government has invested vast resources in evaluating opioid and non-opioid therapies.

2. Ketorolac has strong analgesic potency that may be predicted to surpass that of codeine or tramadol in the 4 comparative trials. Such a match-up seems inappropriate.

3. Due to risks of GI toxicity, use of Ketorolac for longer than 6 days is contra-indicated on the FDA label for this medication.. How these patients with persistent pain should be managed is unclear. This significant limitation in "real-world" clinical practice is obscured by meta-analyses and similar big-data methods, and should be highlighted.

4. Likewise, all NSAIDs, even with acute use, are associated with potentially serious GI toxicity. This side effect is nowhere discussed in the published Review.

5. For acute post-operative pain, it is unclear from the AHRQ report how or in what sense the performance of opioids is “no better” than that of NSAIDs However, the Review notes an abundance of limitations: "Evidence on how comparative effectiveness and harms of opioid therapy for postoperative pain vary according to patient and prescribing factors was lacking. The number of trials was small for each comparison and most trials had small sample sizes...No study conducted within-study or across-study evaluations of subgroup effects. Evidence was too limited to determine effects of different opioid doses (converted into morphine milligram equivalents) on comparative effectiveness and harms...the trials did not evaluate how effectiveness varied in subgroups defined according to the amount of opioid used." **Of note, no trial permitted opioid refills despite study durations up 15 days. This introduces the potential of poorly or uncontrolled pain at final assessment**.

6. Moreover, large retrospective data is presented to demonstrate that compared to persons not prescribed opioids, opioids for acute post-op pain imposes "risks" of

long-term opioid use – 7.7% of patients at 1-year follow-up in one study. The other study described the proportion of patients with opioid fills 90 to 180 days post-surgery (7.1%); opioid use lasting 90+ days in the period from 180 days post-surgery (1.0%) and either 10 or more opioid fills or 120 or more days' supply (0.46%). Such studies cannot ***"adjust for factors not available in administrative claims, such as pain severity, functional status, level of psychiatric distress, or other measures of clinical status following surgery***." [emphasis by the author]

That retrospective evidence was allowed for opioid harms, and disallowed for opioid benefits, is telling. Post-surgical pain is a prevalent origin of chronic, life-altering pain. The discourse in this review stigmatizes patients experiencing persistent pain who require opioid analgesia. This section using retrospective data needs to be deleted.

7. The author must suggest that post-operative use of opioids at one year is ***not*** a "risk", but rather an "incidence". Long-term pain is often a consequence of poor analgesic control in the peri-operative or acute post-operative setting. In most patients, pain that chronicifies is perpetuated by CNS alteration, divorced from peripheral nociceptive input from the original tissue injury. This makes prevention of chronic pain through aggressive analgesic control, which may include opioids, an imperative.

Chronic pain resulting from inadequate control of acute/post-acute pain is **no less iatrogenic** than the recklessly exaggerated opioid use disorder following prescribed opioids. Unlike individuals with OUD for whom efforts are made to ease access to opioid agonist maintenance, patients with chronic pain are punished for needing opioid pain control by the hostile regulatory environment fostered by CDC's 2016 guideline on opioid prescribing in adults with chronic non-cancer pain.

Contrary to the insinuations of the AHRQ report authors, prescription opioid analgesics do NOT "cause" addiction in patients who are not already predisposed by other factors. [Ref 4] When pain in the peri-operative period is sufficient to require opioid analgesia, it is to be expected that a diminishing proportion of patients will need opioid pain control over time, with a smaller subgroup in whom pain has chronicified continued on opioids as the only therapeutic measure that provides sufficient pain management. This reality of practice is ignored – or perhaps deliberately suppressed – in the AHRQ review.

8. Polymorphism may be a sufficiently strong effect to account for the bimodal structure of patient responses to opioids. It is at least plausible that poor metabolizers and

hyper-metabolizers can explain the low effectiveness of low-dose opioids in millions of patients, while “normal” metabolizers experience significantly better outcomes. Although the AHRQ authors references two papers that address these effects, they exclude any serious discussion of their findings. Other papers they do not reference are also pertinent. **[Ref 5 - Ref 8]**

Conclusions

The published version of AHRQ Comparative Effectiveness Review 240 incorporates multiple and disabling errors of analytic methodology. Arguably the authors of this review have also cherry-picked and misinterpreted data in a manner which reflects a profound and unjustified bias against treatment of either acute or chronic pain by means of prescription opioids. For these reasons, the report must be withdrawn immediately for an independent review by professionals qualified in statistical methods and epidemiology. Given the checkered history of this document, representation of patients and their advocates in this review should be considered mandatory.

References:

[Ref 1] Roger Chou, Jesse Wagner, Azrah Y Ahmed, et al, “Treatments for Acute Pain: A Systematic Review”, Agency for Healthcare Research and Quality, AHRQ Publication No. 20(21)-EHC006, December 2020.

[**Ref 2]** Richard A. Lawhern, PhD., AHRQ correspondence by email, subject “Courtesy Copy – Comments Submitted to AHRQ”, September 13, 2020, with attachment.

[Ref 3] Haeuser W, Toelle TR, “Meta-analyses of pain studies: What we have learned,” *Best Practice & Research Clinical Rheumatology* (2015), http://dx.doi.org/10.1016/j.berh.2015.04.021

Abstract

Meta-analysis is a statistical procedure that integrates the results of at least two independent studies. The biggest threats to meta-analysis are publication bias due to missing studies with negative results and low-quality evidence due to methodological limitations imposed by included studies. Tools to improve the quality of meta-analysis have been developed by the Cochrane Collaboration and by the Preferred Reporting Items for Systematic Re-views and Meta-Analyses (PRISMA). Meta-analyses of trials have demonstrated that pain responses in patients with chronic pain, following treatment, are not normally distributed but have a bimodal distribution with the majority of patients having either very little or very good pain relief. The benefit can be detected within 2-4 weeks following drug administration. Further, the efficacy of drug and physical

treatments is hampered by high placebo response rates, with modest average benefits with active treatments over placebo in both parallel and crossover design trials.

[Ref 4] R. A. Moore, S. Derry and P. J. Wiffen "Challenges in design and interpretation of chronic pain trials" British Journal of Anaesthesia 111 (1): 38–45 (2013) doi:10.1093/bja/aet126

[Ref 5] Nora D Volkow, MD, and Thomas A McLellan, Ph.D., "Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies" . *NEMJ* 2016; 374:1253-1263 March 31, 2016]. http://www.nejm.org/doi/full/10.1056/NEJMra1507771

[Ref 6] "Post-Op Opioid Prescribing Often Ignores CYP2D6 Pharmacogenics", December 25, 2020, *Anesthesiology News,* reported by Josh Bloom, "Recognition of Genetic Differences in Opioid Metabolism, Finally" *American Council on Science and Health*, January 3, 2021 https://www.acsh.org/news/2021/01/03/recognition-genetic-differences-opioid-metabolism-finally-15238

[Ref 7] Tom Lynch and Amy Price, "The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Events," *American Family Physician,* August 1, 2007 https://www.practicalpainmanagement.com/treatments/genetic-testing-pain-medicine-future-coming

[Ref 8] Howard S Smith, MD, "Opiod Metabolism" *Mayo Clinic Proceedings,* 2009 Jul; 84(7): 613–624. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2704133/

[Ref 8] Andrea M. Trescot, MD, and Semyon Faynboym, MD "A Review of the Role of Genetic Testing in Pain Medicine", *Pain Physician 2014:17 ISSN 1533-3159*